

Letter to the Editor

IL-13/IL-22-coproducing T cells, a novel subset, are increased in atopic dermatitis

To the Editor:

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease. A considerable body of evidence has shown that T_H2

cells that produce IL-4 and IL-13 play a central role in the pathogenesis of AD, although T_H1 cells that produce IFN- γ also contribute to the chronic phase of AD.¹ Recently, IL-22 was shown to be upregulated in AD.^{2,3} In AD, IL-22 is thought to be primarily secreted by T_H22 cells that do not coproduce IL-17, IL-4, or IFN- γ , suggesting that T_H2 and T_H22 cells are the major T-cell subsets

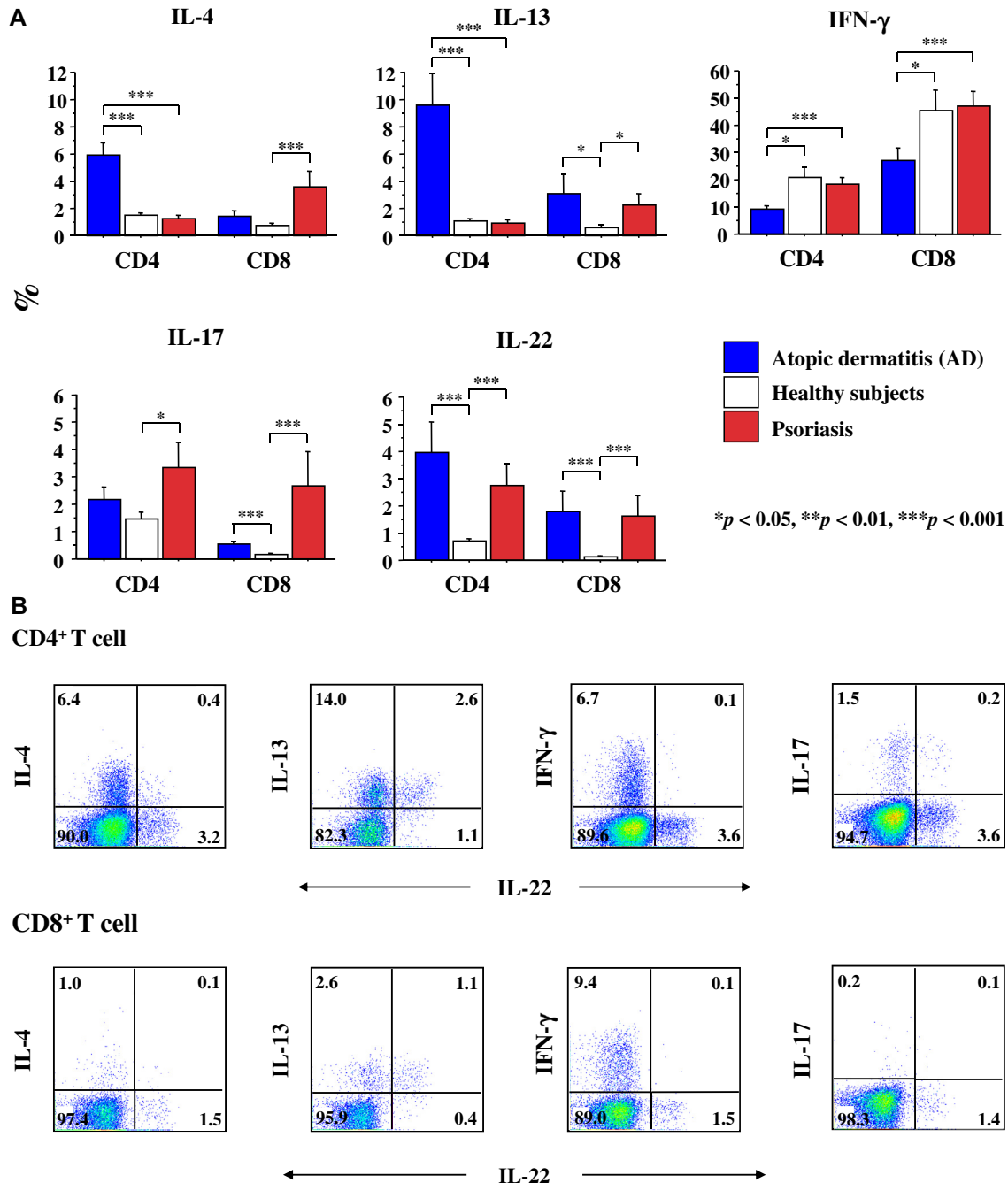


FIG 1. A, Percentage of cytokine-producing T cells among circulating CD4⁺ and CD8⁺ populations in patients with AD (n = 13), patients with psoriasis (n = 10), and healthy subjects (n = 9). **B**, Representative FACS plots for patients with AD. **C**, Proportions of IL-22-producing CD4⁺ and CD8⁺ T cells that coexpress IL-4, IL-13, IL-17, or IFN- γ in patients with AD and psoriasis. Results are relative percentages, with the IL-22-producing cell population set at 100%. FACS, Fluorescence-activated cell sorting.



We next examined the production of IL-4, IL-13, IL-17, and IFN- γ by IL-22-producing T cells in patients with AD and psoriasis (Fig 1, B and C). In agreement with a study that examined AD skin,² only a small proportion of IL-22-producing cells in patients with AD coproduced IL-4, IL-17, and IFN- γ . Strikingly, approximately half of the IL-22-positive CD4⁺ and CD8⁺ T cells in patients with AD coproduced IL-13. In patients with psoriasis, a substantial proportion of IL-22-positive CD4⁺ and CD8⁺ T cells coproduced IL-17 or IFN- γ , but the majority did not coproduce IL-13. The percentage of circulating IL-13/IL-22 double-positive cells was extremely low in healthy subjects

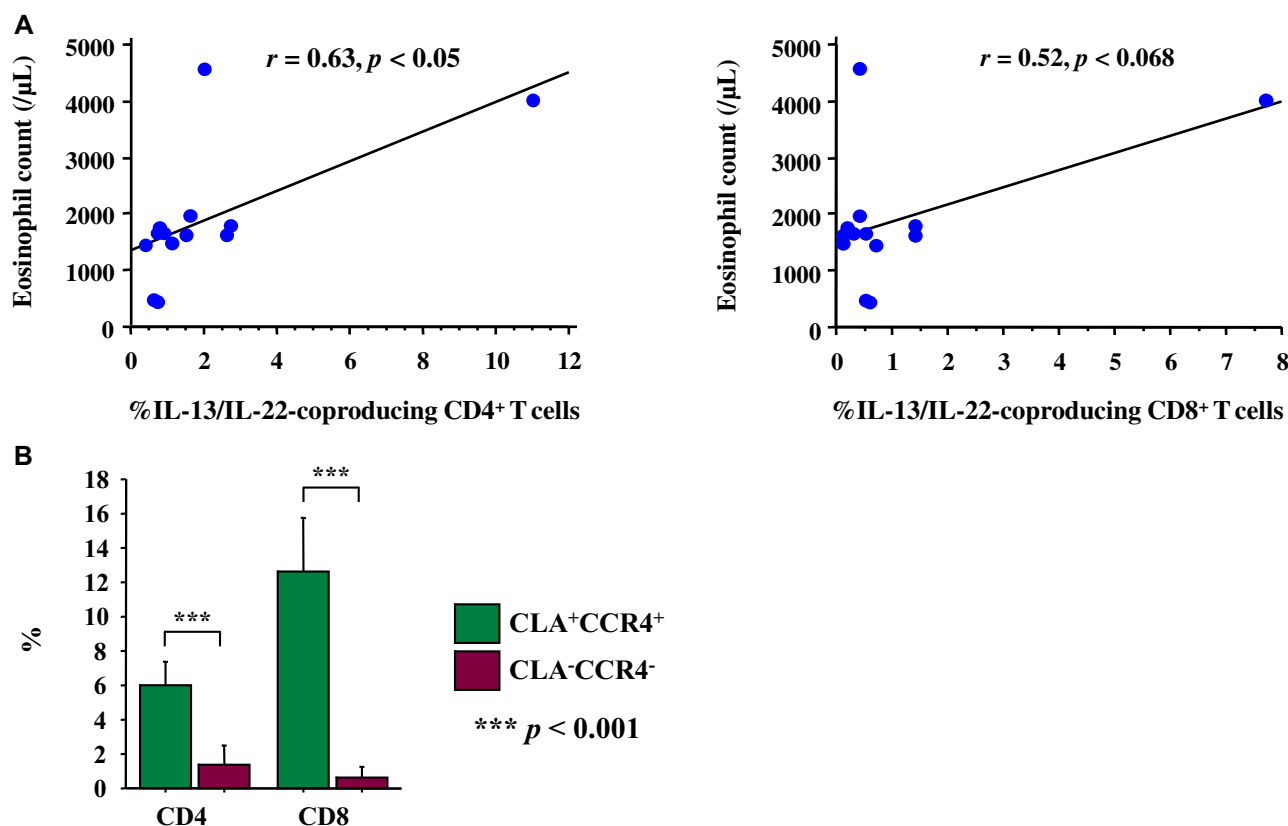


FIG 2. A, Correlations between the eosinophil counts and the percentages of IL-13/IL-22-coproducing CD4⁺ and CD8⁺ T cells in the circulation of patients with AD ($n = 13$). B, Comparison of the percentages of IL-13/IL-22-coproducing cells in the CLA⁺CCR4⁺ and CLA⁻CCR4⁻ subsets among circulating CD4⁺ and CD8⁺ T cells in patients with AD. CLA, Cutaneous lymphocyte antigen; CCR4, CC chemokine receptor 4.

(<0.1%). Although T_H22 and T_H17 cells are considered to be the major T-cell subsets that produce IL-22 in AD skin lesions and psoriatic skin, respectively,^{2,3} our results suggest that IL-13/IL-22-coproducing T cells are the primary source of IL-22 in patients with AD, whereas IFN- γ /IL-22-coproducing cells and T_H17 cells are the primary sources of IL-22 in patients with psoriasis. Thus, circulating IL-13/IL-22-coproducing T cells were increased in patients with AD.

There was a positive correlation between the percentages of IL-13- and IL-22-producing cells for both CD4⁺ and CD8⁺ T-cell populations in patients with AD (CD4, $r = 0.93, P < .001$; CD8, $r = 0.96, P < .001$). This suggested a significant relationship between IL-13 and IL-22 expression in AD.

IL-13 is a critical mediator that affects IgE production and eosinophil survival,¹ and IL-22 promotes keratinocyte proliferation and epidermal hyperplasia⁶ that are observed in AD skin. Therefore, IL-13/IL-22-coproducing T cells may play a key role in the pathogenesis of AD. Indeed, there was a positive correlation between the percentage of IL-13/IL-22-coproducing CD4⁺ T cells ($r = 0.63, P < .05$), not CD8⁺ T cells ($r = 0.52, P = .068$), and the number of eosinophils in the circulation of patients with AD (Fig 2, A), although eosinophil levels are not a specific marker for AD disease severity. There was no significant correlation between the percentages of IL-13/IL-22-coproducing cells and SCORAD (CD4, $r = 0.133, P = .672$; CD8, $r = 0.184,$

$P = .556$). This was probably because all our patients with AD were severe cases.

T_H22 cells were originally identified as circulating T-cell clones that express skin-homing and chemokine receptors: CLA, CCR4, CCR6, and CCR10.^{7,8} In keeping with these reports, the majority of IL-13/IL-22-coproducing CD4⁺ and CD8⁺ T cells belonged to the CLA⁺CCR4⁺ subset in patients with AD (Fig 2, B). This suggests that IL-13/IL-22-coproducing cells have skin-homing capability.

It is now recognized that T_H cells are not restricted with regard to their cytokine production.⁹ For example, under appropriate conditions of stimulation, memory T_H1 cells produce the T_H2-specific cytokine IL-4 and memory T_H2 cells produce the T_H1-specific cytokine IFN- γ . T_H17 cells can also become IFN- γ producers. However, it remains unclear whether T_H22 cells exhibit this plasticity. In this regard, Eyerich et al¹⁰ reported that T_H22 clones represented a stable T-cell lineage; if cultured under T_H1-, T_H2-, T_H17-, or regulatory T cell-polarizing conditions, T_H22 clones continue to express IL-22 and not those cytokines associated with other T_H subsets. However, the presence of IL-13/IL-22- and IFN- γ /IL-22-coproducing cells in patients with AD and psoriasis, respectively, suggests a possible shift from T_H22 to T_H22/T_H2 or T_H22/T_H1 in the skin microenvironment. Thus, IL-22 producers may be heterogeneous and vary in their cytokine production in different inflammatory skin diseases.

In conclusion, we demonstrated an increased proportion of IL-13/IL-22–coproducing T cells with skin-homing properties in the circulation of patients with AD. IL-13/IL-22–coproducing cells represent a novel T-cells subset that may play a key role in the pathogenesis of AD.

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